EXHIBIT E

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden

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ABSTRACT

BACKGROUND

Recent reports have indicated that there may be an increased risk of late stent thrombosis with the use of drug-eluting stents, as compared with bare-metal stents.

METHODS

We evaluated 6033 patients treated with drug-eluting stents and 13,738 patients treated with bare-metal stents in 2003 and 2004, using data from the Swedish Coronary Angiography and Angioplasty Registry. The outcome analysis covering a period of up to 3 years was based on 1424 deaths and 2463 myocardial infarctions and was adjusted for differences in baseline characteristics.

RESULTS

The two study groups did not differ significantly in the composite of death and myocardial infarction during 3 years of follow-up. At 6 months, there was a trend toward a lower unadjusted event rate in patients with drug-eluting stents than in those with bare-metal stents, with 13.4 fewer such events per 1000 patients. However, after 6 months, patients with drug-eluting stents had a significantly higher event rate, with 12.7 more events per 1000 patients per year (adjusted relative risk, 1.20; 95% confidence interval [CI], 1.05 to 1.37). At 3 years, mortality was significantly higher in patients with drug-eluting stents (adjusted relative risk, 1.18; 95% CI, 1.04 to 1.35), and from 6 months to 3 years, the adjusted relative risk for death in this group was 1.32 (95% CI, 1.11 to 1.57).

CONCLUSIONS

Drug-eluting stents were associated with an increased rate of death, as compared with bare-metal stents. This trend appeared after 6 months, when the risk of death was 0.5 percentage point higher and a composite of death or myocardial infarction was 0.5 to 1.0 percentage point higher per year. The long-term safety of drug-eluting stents needs to be ascertained in large, randomized trials.

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Prospective, randomized clinical trials have shown that in-stent restenosis is reduced by the use of drug-eluting stents, as compared with bare-metal stents.[1,2] On the basis of prospective trials involving approximately 4500 patients, the U.S. Food and Drug Administration approved the use of drug-eluting stents for patients with previously untreated coronary lesions of less than 30 mm in length and a reference-vessel diameter of 2.50 to 3.75 mm. In these trials, the use of drug-eluting stents appeared to be safe, with no significant increase in cardiovascular events, as compared with bare-metal stents.[3-6] However, the use of drug-eluting stents has rapidly been expanded to all types of patients, including those with more complicated coronary lesions and in acute settings.

Recently, pathoanatomical studies[7,8] and meta-analyses of randomized trials[9,10] and registries[11] have raised concern about incomplete neointimal coverage with a subsequent increase in late stent thromboses in patients with drug-eluting stents.[12,13] One randomized trial indicated that the implantation of drug-eluting stents was associated with an early reduction in death and myocardial infarction — an improvement that was lost during the subsequent 6 to 18 months by a late increase in the same events.[14] Since there have been no prospective, randomized clinical trials involving long-term follow-up of the "off-label" use of drug-eluting stents,[15] we determined that the evaluation of large clinical registries might provide useful information concerning the long-term efficacy and safety of drug-eluting stents. Therefore, we evaluated the long-term outcome in all patients who underwent stent implantation in Sweden in 2003 and 2004, as recorded in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), and conducted a follow-up analysis of death and myocardial infarction, using other national registries.

METHODS

STUDY POPULATION

Our study included all patients in Sweden who had received coronary stents from January 1, 2003, to December 31, 2004, for whom complete follow-up data were available from other national registries. The analyses were based on the type of stent implanted at the first recorded procedure, in which patients who received at least one drug-eluting stent were assigned to the drug-eluting–stent group, regardless of whether they had received another type of stent at any time; otherwise, patients were assigned to the bare-metal–stent group. In a sensitivity analysis, we separately evaluated the cohort of patients who had received only one stent (the one-stent subgroup) at the initial percutaneous coronary intervention (PCI).

SCAAR DATA

SCAAR holds data on consecutive patients from all 26 centers that perform coronary angiography and PCI in Sweden. The registry is sponsored by the Swedish Health Authorities and is independent of commercial funding. The technology is developed and administered by the Uppsala Clinical Research Center. Since 2001, SCAAR has been Internet-based, with recording of data online through a Web interface in the catheterization laboratory; data are transferred in an encrypted format to a central server at the Uppsala Clinical Research Center. All consecutive patients undergoing coronary angiography or PCI are included. We compiled a list of the most important recorded variables in accordance with international recommendations (Table 1).[16] Information with respect to restenosis has been registered for patients undergoing subsequent coronary angiography for clinical reasons since the beginning of 2004. The Internet-based system provides each center with immediate and continuous feedback on processes and quality-of-care measures. Monitoring and verification of registry data have been performed in all hospitals since 2001 by comparing 50 entered variables in 20 randomly selected interventions per hospital and year with the patients' hospital records. The overall correspondence in data during the study period was 95.2%. By December 31, 2005, information on approximately 255,000 procedures had been collected in SCAAR.

The long-term follow-up was based on merging the SCAAR database with other national registries on the basis of the unique 10-digit personal identification number of each Swedish citizen. Data on vital status and date of death were obtained from the national population registry through June 30, 2006. We obtained data regarding hospital admissions for myocardial infarction (as defined in the *International Classification of Diseases*, 10th revision, disease codes, I21 and I22)

from the Swedish Hospital Discharge Registry through December 31, 2005, except for one small county (with 417 patients) in which myocardial infarction could be evaluated only through December 31, 2004. The merging of the registries was performed by the Epidemiologic Center of the Swedish National Board of Health and Welfare and was approved by the local ethics committee at Uppsala University.

STATISTICAL ANALYSIS

We summarized baseline characteristics of the patients with medians and interquartile ranges for continuous variables and percentages for discrete variables. Cumulative event rates were estimated by the Kaplan–Meier method. The primary objective was to evaluate late-occurring events after the implantation of drug-eluting stents. The primary end point was the composite of death or myocardial infarction. Secondary end points were death, myocardial infarction, revascularization, and restenosis. To compensate for the nonrandomized design of our observational study, we used propensity-score methods.[17] The individual propensity scores, defined as the conditional probability of obtaining a drug-eluting stent based on available covariables, were estimated with a multiple logistic-regression model. All prespecified covariates were included in the respective models for the two study populations as well as several interaction terms (Table 1). The predictive ability of each propensity-score model was evaluated by means of the C statistic.

To provide separate descriptions of the early and late relative risks of events, we performed a "landmark analysis"[18] with a prespecified landmark set at 6 months. Adjusted relative risks were estimated from models in which the propensity score and the stent group were entered as covariates. For plotting purposes, the models were then refitted with the stent group as a stratification variable, and adjusted cumulative event rates were estimated at the overall average propensity score. Further addition of any of the variables that had already been incorporated through the propensity score did not materially alter the results. Death was regarded as a censoring event in the analysis of myocardial infarction. This analysis led to results that were similar to those obtained when the cumulative incidence of myocardial infarction was estimated in a competing-risks framework (data not shown). All reported P values are two-sided. All analyses were performed with the use of the statistical program R, version 2.4.0.[19]

RESULTS

CHARACTERISTICS OF THE PATIENTS

During 2003 and 2004, a total of 19,771 patients were treated with 37,750 stents in 24,215 PCI procedures in Sweden and were entered into the database. Table 1 shows the characteristics of the 6033 patients with drug-eluting stents and 13,738 patients with bare-metal stents. The factor with the largest influence on the choice of stent was the geographic region. The use of drug-eluting stents ranged from 0.4 to 62.5% among centers and from 0.6 to 40.8% among geographic regions. On average, as compared with patients who received bare-metal stents, patients with drug-eluting stents were slightly younger and were more likely to be women; they also had a higher prevalence of diabetes mellitus, hypertension, heart failure, and renal dysfunction, and stable angina was more likely to be the indication for the procedure. Among patients with drug-eluting stents, pretreatment with clopidogrel was more common, but the periprocedural use of glycoprotein IIb/IIIa inhibitors was less common. In the group with drug-eluting stents, more patients had undergone PCIs and coronary-artery bypass grafting (CABG), had multivessel and left main coronary artery disease, and had a higher number of implanted stents. Patients with bare-metal stents were older, were more likely to be men, and more often had primary PCIs for myocardial infarction with ST-segment elevation as the indication for receiving a stent. In the one-stent subgroup, the drug-eluting stents were generally longer and had smaller diameters than the bare-metal stents. Among the 3638 patients with drug-eluting stents in the one-stent subgroup, paclitaxel-eluting stents (Taxus Express, Boston Scientific) were used in 2608 patients (72%) and sirolimus-eluting stents (Cypher and Cypher Select, Cordis, Johnson & Johnson) in 1030 patients (28%).

DEATH AND MYOCARDIAL INFARCTION

During the entire study period, 3887 events occurred, including 2463 myocardial infarctions (1713 in the group with bare-metal stents and 750 in the group with drug-eluting stents) and 1424 deaths (999 in the group with bare-metal stents

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Table 1. Characteristics of All Patients and the One-Stent Subgroup.*

Variable	All Patients with Stents			One-Stent Subgroup		
	Total†	Bare-Metal Stent (N=13,738)	Drug-Eluting Stent (N=6033)	Total†	Bare-Metal Stent (N=10,319)	Drug-Eluting Stent (N=3638)
	no.			*no.*		
Age	19,771			13,957		
Median — yr		66	65		65	64
Interquartile range — yr		58–74	57–73		57–74	56–72
Female sex — no. (%)	19,771	3,774 (27.5)	1753 (29.1)	13,957	2,873 (27.8)	1106 (30.4)
Hospital region — no. (%)	19,771			13,957		
North		1,704 (12.4)	148 (2.5)		1,281 (12.4)	78 (2.1)
Stockholm		2,539 (18.5)	1010 (16.7)		1,941 (18.8)	589 (16.2)
Southeast		1,396 (10.2)	792 (13.1)		1,206 (11.7)	573 (15.8)
South		2,427 (17.7)	1686 (27.9)		1,685 (16.3)	953 (26.2)
Middle		3,636 (26.5)	2386 (39.5)		2,788 (27.0)	1439 (39.6)
West		2,036 (14.8)	11 (0.2)		1,418 (13.7)	6 (0.2)
Indication — no. (%)	19,420			13,682		
Stable coronary artery disease		3,029 (22.5)	1805 (30.3)		2,210 (21.9)	1081 (30.2)
Unstable coronary artery disease		6,919 (51.4)	3122 (52.5)		5,205 (51.5)	1827 (51.0)
STEMI		3,423 (25.4)	955 (16.1)		2,610 (25.8)	633 (17.7)
Other		100 (0.7)	67 (1.1)		77 (0.8)	39 (1.1)
Smoking staus — no. (%)	19,657			13,863		
Current smoker		2,875 (21.0)	1129 (18.8)		2,188 (21.3)	693 (19.2)
Former smoker		4,240 (31.0)	1858 (31.0)		3,118 (30.4)	1111 (30.8)
Never smoked		4,854 (35.5)	2465 (41.1)		3,666 (35.7)	1469 (40.7)
Unknown		1,694 (12.4)	542 (9.0)		1,283 (12.5)	335 (9.3)
Diabetes — no. (%)	19,771	2,140 (15.6)	1421 (23.6)	13,957	1,618 (15.7)	855 (23.5)
Hypertension — no. (%)	19,656	5,961 (43.6)	2780 (46.4)	13,861	4,368 (42.6)	1614 (44.7)
Previous PCI — no. (%)	19,343	1,393 (10.4)	929 (15.6)	13,631	1,068 (10.6)	606 (16.9)
Previous CABG — no. (%)	19,216	1,296 (9.8)	664 (11.2)	13,532	948 (9.5)	384 (10.7)
Previous myocardial infarction — no. (%)	19,771	5,046 (36.7)	2302 (38.2)	13,957	3,693 (35.8)	1338 (36.8)
Aspirin before procedure — no. (%)	19,763	11,521 (83.9)	5354 (88.8)	13,953	8,542 (82.8)	3161 (86.9)
Clopidogrel — no. (%)	19,729	7,117 (51.9)	3614 (60.1)	13,929	5,248 (51.0)	2085 (57.4)
Cancer <3 yr before procedure — no. (%)	19,656	389 (2.8)	160 (2.7)	13,878	275 (2.7)	89 (2.5)
Previous heart failure — no. (%)	19,771	963 (7.0)	489 (8.1)	13,957	681 (6.6)	271 (7.4)
Previous stroke — no. (%)	19,771	801 (5.8)	374 (6.2)	13,957	586 (5.7)	214 (5.9)
Previous renal failure — no. (%)	19,771	124 (0.9)	79 (1.3)	13,957	80 (0.8)	51 (1.4)
Previous dialysis — no. (%)	19,771	46 (0.3)	40 (0.7)	13,957	28 (0.3)	30 (0.8)
Previous COPD — no. (%)	19,771	628 (4.6)	257 (4.3)	13,957	466 (4.5)	152 (4.2)
Previous dementia — no. (%)	19,771	13 (0.1)	2 (<0.1)	13,957	10 (0.1)	2 (<0.1)
Glycoprotein IIb/IIIa inhibitors — no. (%)	19,724	4,978 (36.3)	1900 (31.6)	13,927	3,646 (35.4)	1101 (30.4)

Table 1. (Continued.)

Variable	All Patients with Stents			One-Stent Subgroup		
	Total†	Bare-Metal Stent (N=13,738)	Drug-Eluting Stent (N=6033)	Total†	Bare-Metal Stent (N=10,319)	Drug-Eluting Stent (N=3638)
	no.			*no.*		
No. of stents — no. (%)	19,757			13,957		
1		10,319 (75.2)	3638 (60.3)		10,319 (100)	3638 (100)
2		2,574 (18.8)	1680 (27.9)		0	0
≥3		833 (6.1)	713 (11.8)		0	0
Findings on angiography — no. (%)	19,271			13,577		
Not significant		35 (0.3)	16 (0.3)		31 (0.3)	11 (0.3)
1-vessel disease		6,816 (51.2)	2813 (47.2)		5,706 (57.2)	2150 (59.8)
2-vessel disease		3,765 (28.3)	1778 (29.8)		2,459 (24.6)	788 (21.9)
3-vessel disease		2,199 (16.5)	1069 (17.9)		1,439 (14.4)	505 (14.1)
Left main coronary artery disease (with or without other coronary disease)		491 (3.7)	289 (4.8)		349 (3.5)	139 (3.9)
Stent diameter — no. (%)				13,890		
<2.5 mm					337 (3.3)	328 (9.1)
2.5 to <3.0 mm					2,314 (22.5)	1203 (33.3)
3.0 to <3.5 mm					3,897 (37.9)	1311 (36.2)
3.5 to <4 mm					2,663 (25.9)	744 (20.6)
≥4 mm					1,061 (10.3)	32 (0.9)
Stent length — no. (%)				13,910		
<10 mm					864 (8.4)	182 (5.0)
10–14 mm					3,074 (29.9)	792 (21.8)
15–16 mm					2,767 (26.9)	796 (21.9)
17–19 mm					1,313 (12.8)	341 (9.4)
20–23 mm					1,092 (10.6)	675 (18.6)
24–25 mm					716 (7.0)	382 (10.5)
26–30 mm					304 (3.0)	187 (5.2)
≥31 mm					153 (1.5)	272 (7.5)
Restenotic lesion — no. (%)				13,877	121 (1.2)	243 (6.7)
Treated vessel — no. (%)				13,951		
Right coronary artery					3,463 (33.6)	557 (15.3)
Left main coronary artery					99 (1.0)	82 (2.3)
Left anterior descending artery					3,969 (38.5)	2260 (62.1)
Left circumflex artery					2,386 (23.1)	619 (17.0)
CABG graft					397 (3.8)	119 (3.3)

* PCI denotes percutaneous coronary intervention, CABG coronary-artery bypass grafting, STEMI myocardial infarction with ST-segment elevation, and COPD chronic obstructive pulmonary disease. Percentages may not total 100 because of rounding.
† Values indicate the number of patients for whom data were available for each variable.

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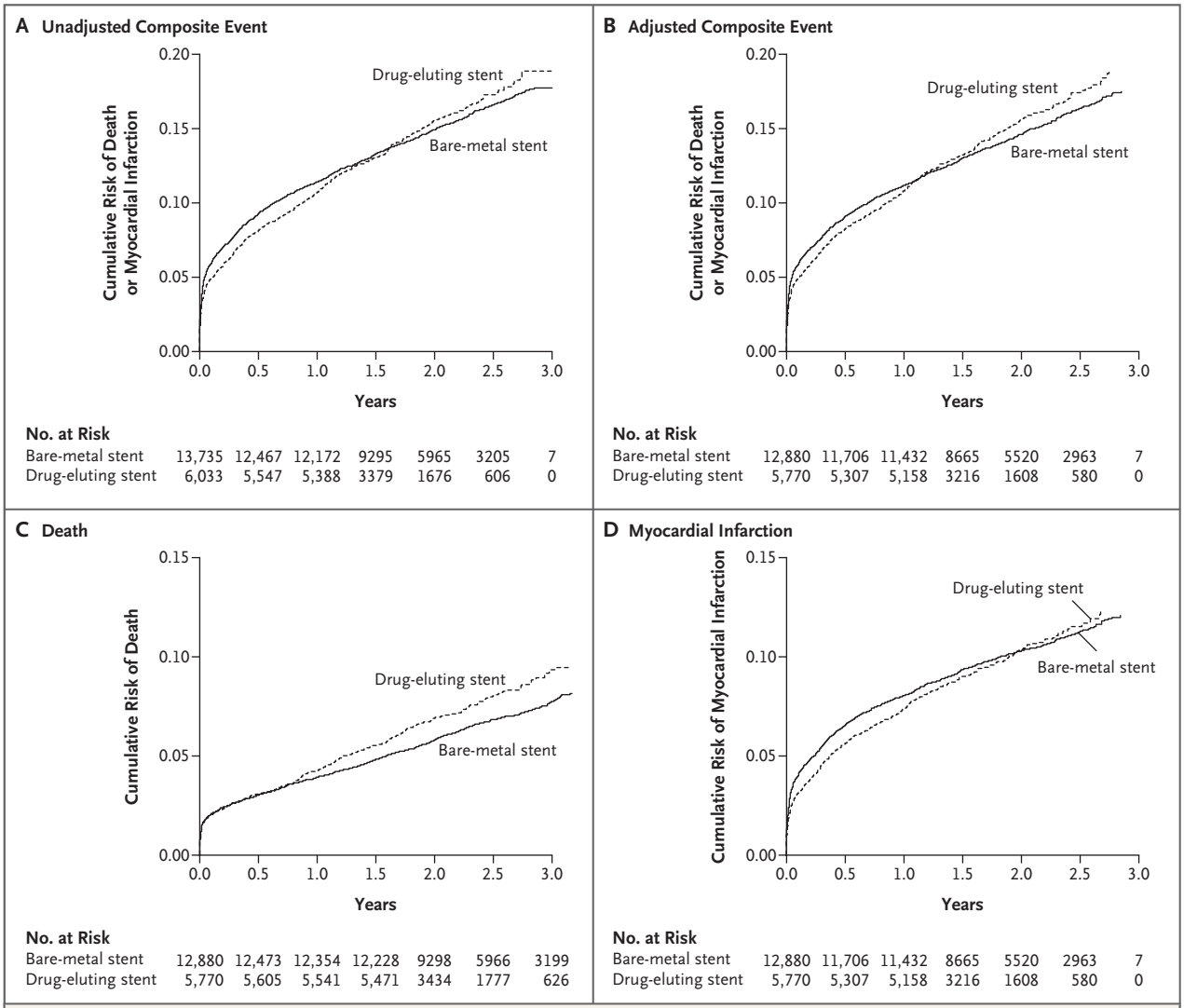

Figure 1. Estimated Cumulative Event Rates.

Panel A shows unadjusted composite event data for 3 years of follow-up. In Panels B, C, and D, the curves represent estimations from the Cox regression model at the mean level of the propensity score. Numbers of patients at risk are shown below each graph.

and 425 in the group with drug-eluting stents). There was no significant difference between the two groups in the composite risk of death and myocardial infarction during the 3-year follow-up period (Fig. 1A and 1B). At 6 months, there was an indication of a lower unadjusted event rate in the group with drug-eluting stents than in the group with bare-metal stents, with 13.4 fewer events per 1000 patients. However, during continued follow-up, there was a higher unadjusted event rate in the group with drug-eluting stents, with 12.7 more events per 1000 patients per year.

Accordingly, in the landmark analysis, the adjusted event rate tended to be lower in the group with drug-eluting stents during the initial 6 months (Fig. 2A). Thereafter, there was a continuous separation of the curves, with a significantly higher rate of events in patients with drug-eluting stents (relative risk, 1.20; 95% confidence interval [CI], 1.05 to 1.37). In the one-stent subgroup, allowing for adjustment for characteristics of both stents and lesions, the outcome was similar, with a lower risk of death or myocardial infarction in the group with drug-eluting stents during the first 6 months (relative risk, 0.82; 95% CI, 0.69 to 0.98) and a higher risk after the first 6 months (relative risk,

1.23; 95% CI, 1.02 to 1.48) (Fig. 3A). There were no significant differences in early outcome (P=0.40) or late outcome (P=0.30) between patients with paclitaxel-eluting stents and those with sirolimus-eluting stents.

RISK OF DEATH

Propensity-score–adjusted Cox regression analysis showed a significantly higher risk of death in the group with drug-eluting stents than in the group with bare-metal stents (relative risk, 1.18; 95% CI, 1.04 to 1.35) (Fig. 1C). At 6 months, the risk of death was similar in the two groups (Fig. 2B). However, after 6 months, the risk of death was significantly higher in the group with drug-eluting stents, with a continuous separation of the events curves (relative risk, 1.32; 95% CI, 1.11 to 1.57).

MYOCARDIAL INFARCTION

At 6 months, the adjusted cumulative risk of myocardial infarction was lower in the group with drug-eluting stents (Fig. 1D, 2C, and 3C). However, between 6 and 12 months, the risk of myocardial infarction was higher in the group with drug-eluting stents. Accordingly, in the landmark analysis, the event curves diverged over time, and after 6 months, there was a nonsignificant trend toward an increased risk of myocardial infarction both in the overall population (relative risk, 1.12; 95% CI, 0.95 to 1.32) and in the one-stent subgroup (relative risk, 1.18; 95% CI, 0.93 to 1.49).

NEW REVASCULARIZATION AND RESTENOSIS

During follow-up, in the group with drug-eluting stents, 888 patients (14.7%) had new PCIs, 92 patients (1.5%) had coronary surgery, and 917 patients (15.2%) had new revascularization; in the group with bare-metal stents, 1989 patients (14.5%) had new PCIs, 403 patients (2.9%) had coronary surgery, and 2260 patients (16.5%) had new revascularization. Among the 2285 patients receiving a second stent, the median time to a repeated PCI was 138 days for both groups, but 558 of 710 patients (78.6%) in the group with drug-eluting stents received new drug-eluting stents, as compared with 869 of 1575 patients (55.2%) in the group with bare-metal stents. In a Cox regression analysis, as compared with the group with bare-metal stents, the group with drug-eluting stents had a lower adjusted risk of undergoing a new PCI (rel-

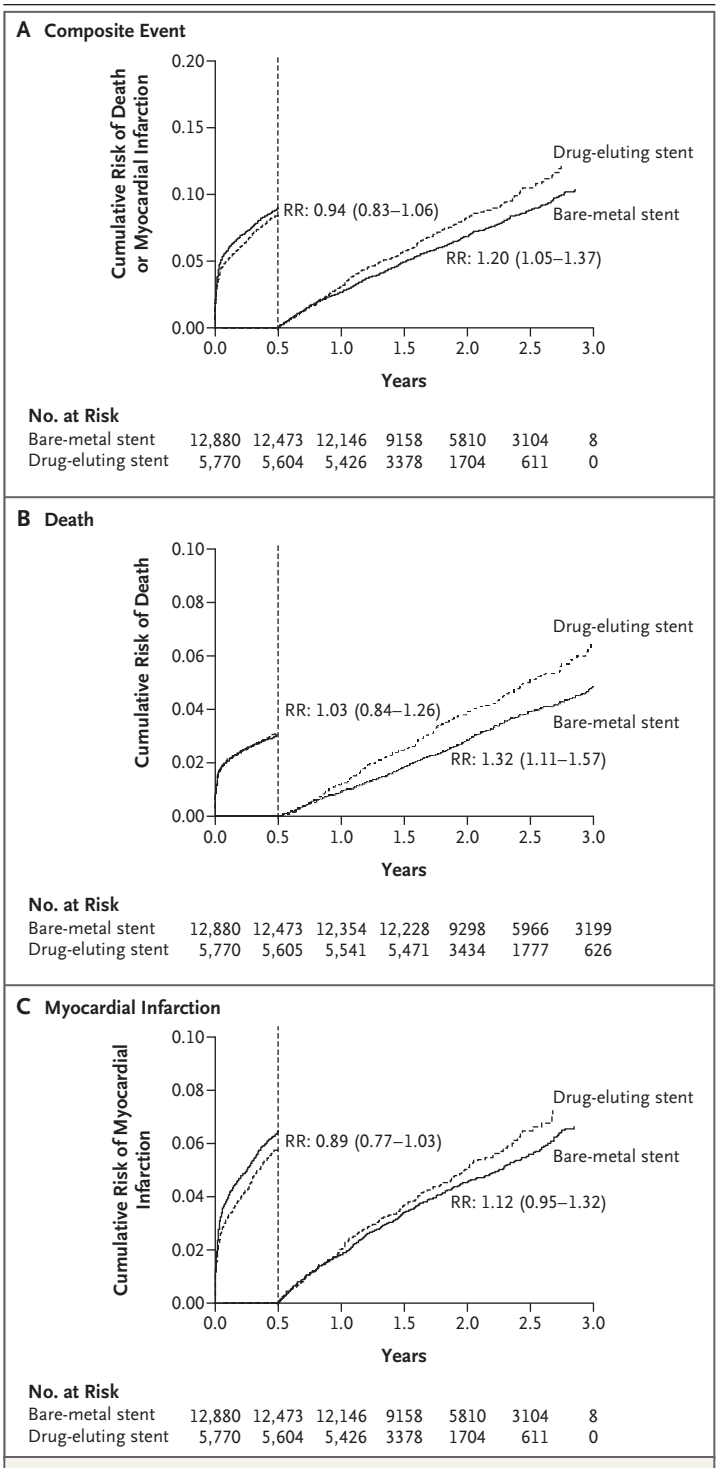

Figure 2. Landmark Analysis of All Study Patients.

Panels A, B, and C show propensity-score–adjusted cumulative event rates at the mean level of the propensity score during the first 6 months after stent placement and after the first 6 months, for all patients. Risk ratios (with 95% CIs) are for the occurrence of an event among patients with drug-eluting stents, as compared with those with bare-metal stents.

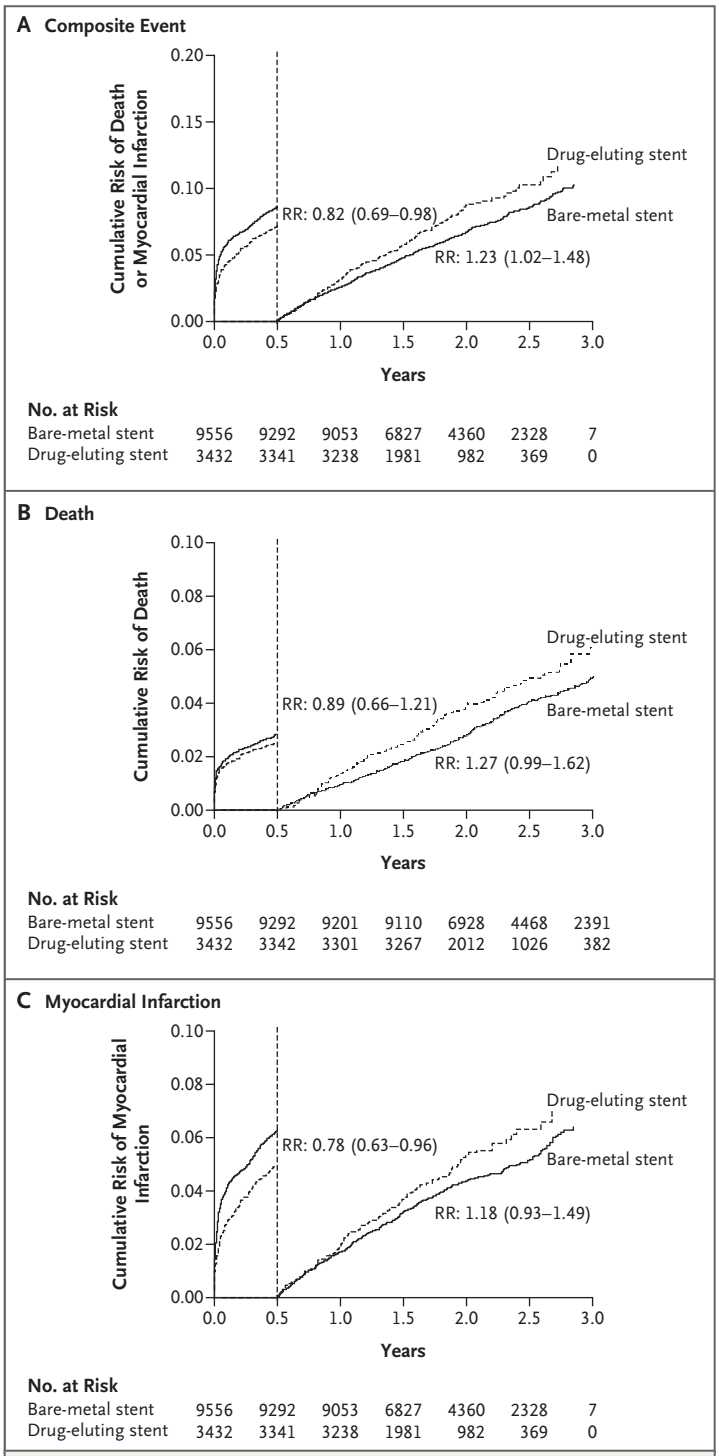

Figure 3. Landmark Analysis of the One-Stent Subgroup.

Panels A, B, and C show propensity-score–adjusted cumulative event rates at the mean level of the propensity score during the first 6 months after stent placement and after the first 6 months, for patients with only one stent. Risk ratios (with 95% CIs) are for the occurrence of an event among patients with drug-eluting stents, as compared with those with bare-metal stents.

ative risk, 0.90; 95% CI, 0.82 to 0.98), CABG (relative risk, 0.54; 95% CI, 0.42 to 0.70), or any new revascularization (relative risk, 0.84; 95% CI, 0.77 to 0.92). Among 4587 patients with drug-eluting stents implanted in 2004, restenosis was registered in 165 (3.6%), as compared with 447 of 7564 patients (5.9%) with bare-metal stents. In a Cox regression analysis, the adjusted risk of restenosis was significantly lower in patients with drug-eluting stents than in those with bare-metal stents (relative risk, 0.40; 95% CI, 0.31 to 0.51).

DISCUSSION

Our study compared the long-term outcome of drug-eluting stents versus bare-metal stents in a large cohort of unselected consecutive patients treated with coronary stents at all interventional centers in Sweden. The data are entered into SCAAR to be used as tools for the treatment of patients, which improves the reliability of such information. The validity was also supported by source-data verification, which had a 95% correspondence with patients' hospital records. The long-term follow-up was complete, since it was based on merging the SCAAR database with the national registries of vital statistics and of hospital admissions. Although the nonrandomized comparison between the study groups was adjusted for all available confounders, there is always a possibility of selection bias because of unknown confounders. However, in our study, the major reason for the selection of drug-eluting stents or bare-metal stents was the large variation in acceptance of the indications for these devices among the hospitals and geographic regions. Therefore, the selection of either type of device was often at random in relation to patient-related factors, which led to the opportunity to compare the group with drug-eluting stents with a contemporary, at least partly nonselected control group of patients with bare-metal stents.

Comparisons between nonrandomized groups usually are based on Cox regression analyses with adjustment for differences in all available background factors between the groups. However, these analyses require proportional hazards over time in order to make formal statistical comparisons between the groups appropriate. Therefore, the time course of events over the entire follow-up period was illustrated with unadjusted and propensity-score–adjusted cumulative event rates.

For the matter of statistical inference, the groups were compared in landmark analyses with an offset at 6 months. We had two reasons for choosing a 6-month cutoff. First, the recommendation for the duration of clopidogrel treatment after stent placement is up to 6 months in most centers in Sweden. Second, despite initial differences in event rates between the main indications (myocardial infarction with ST-segment elevation, the acute coronary syndrome, and stable coronary artery disease), after 6 months the event rates became similar for all three main-indication groups. By this division in early and late risk, we also overcame the problem with nonproportional hazards, which allowed for the estimation of relative risks and confidence intervals. A similar approach was used by Eisenstein at al.[20]

Our study showed an increased long-term risk of death among patients with drug-eluting stents, as compared with patients with bare-metal stents, stemming from an increased risk of death after 6 months. When evaluating the event rates in the landmark analysis starting at 6 months, we found an approximate 30% increase in the risk of death, and it remained consistent over time. Concerning the composite of death and myocardial infarction, there was a trend toward a lower event rate during the initial 6 months and a consistently higher event rate thereafter. These findings were best demonstrated by the results in the one-stent subgroup, in which adjustment could be made for differences in lesion-related characteristics. Among patients with drug-eluting stents, this subgroup had a relatively lower composite event rate (18%) during the first 6 months but thereafter had a relatively higher rate (23%). This early gain and late loss in the composite event rate might have been related to the risk of stent-related thrombosis with drug-eluting stents that was initially lower and later higher than that with bare-metal stents. This finding corresponds to the results of a recent randomized trial.[14]

According to criteria recently proposed by the Academic Research Consortium, the late events in our study would correspond to "possible stent thrombosis." The time course of these events also corresponds to the recent reports from the meta-analyses of randomized trials[9,10,14] and registries.[14] The likelihood that these events were caused by stent thrombosis is strengthened by the demonstration of incomplete neointimal coverage as a probable reason for late stent thromboses in patients with drug-eluting stents.[12,13] Although stent thromboses seem to occur only in approximately 0.5% of patients treated with drug-eluting stents per year, this factor may still have an effect on the risk of death, since a fatal outcome has been reported in up to 45% of these patients.[21] Our findings are a cause for worry, since they indicate a continuous increase of approximately 0.5% per year in the risk of death and an increase of 0.5 to 1.0% per year in the incidence of death or myocardial infarction after 6 months. If this increased risk is maintained during even longer periods than the 3 years of follow-up in our study, any initial gains in event rates will be superseded by the continuous loss in late events.

The increase in event rate was observed only after the first 6 months. Although no details on long-term use of clopidogrel are available, most patients were prescribed dual antiplatelet treatment for 6 months after implantation of drug-eluting stents but for only 1 to 3 months after implantation of bare-metal stents. Therefore, the early gain and late loss of clinical events in the group with drug-eluting stents might have been related to better protection with clopidogrel in the early phase and a prolonged need for such protection after 6 months. It has been proposed that the occurrence of late stent thrombosis may be due to delayed healing[7,22] that may necessitate lifelong dual antiplatelet therapy. Such an interpretation is in accordance with the recently reported high rates of death and myocardial infarction in patients with drug-eluting stents after cessation of clopidogrel, from the Duke database.[20]

The average rate of use of drug-eluting stents increased substantially during the study period, but there remained a large variation among the centers and indications. Although geographic differences accounted for most of the differences in the use of drug-eluting stents, patient selection was also based on risk criteria for restenosis, as suggested by the higher percentage of clinical and angiographic high-risk features in patients with drug-eluting stents.[23] The clinical restenosis rate was approximately 60% lower among patients with drug-eluting stents than among patients with bare-metal stents. However, the restenosis rate after the implantation of bare-metal stents (5.9%) and the absolute differences in the rates of restenosis (3%) and reintervention (1%) between the two groups were lower in our study than in randomized clinical trials and in other registry

data.[24-26] The low incidence of restenosis and reintervention after the implantation of bare-metal stents and the small difference after the implantation of drug-eluting stents do not support the need for drug-eluting stents in patients at low or intermediate risk for restenosis.

Despite our use of appropriate statistical adjustments, differences in baseline characteristics or selection criteria that might not have been recorded could remain. Potential alternative explanations exist for the crossing of event curves — for example, multiple selection biases, such as higher early-event rates in patients with bare-metal stents because of a higher proportion of patients with myocardial infarction with ST-segment elevation and higher late-event rates in patients with drug-eluting stents because of a higher proportion of high-risk patients. Also, changes in event rates over time might have been influenced by the smaller number of patients with drug-eluting stents early in the study period. Another limitation is the lack of information about the duration of clopidogrel treatment in individual patients.

In conclusion, we showed that patients with drug-eluting stents had an 18% increase in the relative long-term risk of death, as compared with patients with bare-metal stents — an increase that corresponded to an absolute increase of 0.5% in the risk of death per year after the initial 6 months. The analysis of the composite of death and myocardial infarction indicated a lower event rate during the first 6 months but thereafter an increase of approximately 20%, which corresponded to an absolute increase of 0.5 to 1.0% per year. Although the rate of clinically observed restenosis was 60% lower among patients with drug-eluting stents, the absolute difference did not amount to more than 3%. Therefore, a generalized, unselective use of drug-eluting stents should be avoided until randomized studies with an adequate number of patients and long-term follow-up have ruled out any increased long-term risk. Such studies should also provide clear evidence about the duration of dual antiplatelet therapy and the risk–benefit ratio in subgroups of patients based on clinical and angiographic risk criteria.

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APPENDIX

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ORIGINAL ARTICLE

Safety and Efficacy of Sirolimus- and Paclitaxel-Eluting Coronary Stents

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ABSTRACT

BACKGROUND

The safety of drug-eluting stents has been called into question by recent reports of increased stent thrombosis, myocardial infarction, and death. Such studies have been inconclusive because of their insufficient size, the use of historical controls, a limited duration of follow-up, and a lack of access to original source data.

METHODS

We performed a pooled analysis of data from four double-blind trials in which 1748 patients were randomly assigned to receive either sirolimus-eluting stents or bare-metal stents and five double-blind trials in which 3513 patients were randomly assigned to receive either paclitaxel-eluting stents or bare-metal stents; we then analyzed the major clinical end points of the trials.

RESULTS

The 4-year rates of stent thrombosis were 1.2% in the sirolimus-stent group versus 0.6% in the bare-metal–stent group (P=0.20) and 1.3% in the paclitaxel-stent group versus 0.9% in the bare-metal–stent group (P=0.30). However, after 1 year, there were five episodes of stent thrombosis in patients with sirolimus-eluting stents versus none in patients with bare-metal stents (P=0.025) and nine episodes in patients with paclitaxel-eluting stents versus two in patients with bare-metal stents (P=0.028). The 4-year rates of target-lesion revascularization were markedly reduced in both the sirolimus-stent group and the paclitaxel-stent group, as compared with the bare-metal–stent groups. The rates of death or myocardial infarction did not differ significantly between the groups with drug-eluting stents and those with bare-metal stents.

CONCLUSIONS

Stent thrombosis after 1 year was more common with both sirolimus-eluting stents and paclitaxel-eluting stents than with bare-metal stents. Both drug-eluting stents were associated with a marked reduction in target-lesion revascularization. There were no significant differences in the cumulative rates of death or myocardial infarction at 4 years.

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By reducing neointimal hyperplasia after vascular injury, drug-eluting coronary-artery stents decrease late luminal loss (the difference between the minimal luminal diameter immediately after the procedure and the diameter at 6 months) and angiographic restenosis, as compared with bare-metal stents. This decrease, in turn, reduces the need for subsequent revascularization procedures.[1-9] Despite these benefits, drug-eluting stents may engender adverse arterial responses, including delayed endothelialization and hypersensitivity to the polymeric coating that regulates drug dose and release kinetics.[10-13] Recent reports from randomized trials and observational studies using historical controls have suggested that drug-eluting stents may be associated with increased rates of late stent thrombosis and death, as compared with bare-metal stents.[14-17] These studies have been inconclusive, however, because of an insufficient number of patients, the absence of concurrent controls, a limited duration of follow-up, and a lack of access to original source data. Since more than 1 million of these permanent bioactive devices are implanted in patients annually, understanding the relative safety and efficacy of drug-eluting stents represents a major public health imperative.

To address the limitations of previous studies, we performed a pooled analysis of data from four double-blind trials in which patients were randomly assigned to receive polymer-based sirolimus-eluting stents or bare-metal stents and five double-blind trials in which patients were randomly assigned to receive polymer-based paclitaxel-eluting stents or bare-metal stents. We report on the safety and efficacy of drug-eluting stents with 4-year follow-up after device implantation.

METHODS

STUDY DESCRIPTION

The databases from four prospective, multicenter, double-blind, placebo-controlled randomized trials of sirolimus-eluting stents versus bare-metal stents were obtained from Cordis. These trials were the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary-Artery Lesions (RAVEL), the Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary-Artery Lesions (SIRIUS), and the smaller European and Latin American (E-SIRIUS) and Canadian (C-SIRIUS) trials.[1-4] Similarly, the databases from five prospective, multicenter, double-blind, placebo-controlled, randomized trials of paclitaxel-eluting stents versus bare-metal stents were obtained from Boston Scientific. These trials consisted of the studies TAXUS-I, TAXUS-II, TAXUS-IV, TAXUS-V, and TAXUS-VI.[5-9] These specific trials were selected because they are the only double-blind trials that compared each of the drug-eluting stents with bare-metal controls and that also served as the basis for the approval of the drug-eluting stents in the United States and Europe. In both cases, permission was obtained for the performance of an unrestricted, patient-level pooled analysis.

Details of the design and conduct of each of the trials included in these analyses have been reported previously.[1-9] In each trial, patients with a single previously untreated native coronary-artery lesion were prospectively and randomly assigned in equal proportion to receive either a drug-eluting stent or an otherwise equivalent bare-metal stent. Entry criteria, device specifications, and geographic location varied somewhat, as outlined in Table 1. At the time of this report, the patients, investigators, study personnel, and sponsors were still unaware of assignments to study groups, with follow-up continuing to 5 years. Data regarding the use of aspirin and a thienopyridine were not consistently captured during follow-up. However, data on the use of antiplatelet drugs at the time of late thrombosis associated with drug-eluting stents were obtained from the manufacturers of both drug-eluting stents. No agreements with the sponsors regarding data confidentiality exist.

END POINTS AND DEFINITIONS

The goals of our study were to determine the short-term and long-term safety and efficacy of drug-eluting stents as compared with bare-metal stents. Before receiving the study databases, we specified that we would examine the following end points: stent thrombosis, as defined in the study protocols (see the Supplementary Appendix, available with the full text of this article at www.nejm.org)[1-9]; revascularization of the target lesion or target vessel; any myocardial infarction and Q-wave and non–Q-wave myocardial infarction; death from any cause and from cardiac and noncardiac causes; composite death or myocardial infarction; composite death or Q-wave myocardial infarction; and composite death from car-

Table 1. Characteristics of the Study Trials.

Trials*	Number of Patients	Geographic Location	Stent Platform	Drug-Release Kinetics	Reference-Vessel Diameter	Lesion Length	Minimum Administration of Clopidogrel	Clinical Follow-up Attained	Routine Angiographic Follow-up
					mm		*mo*		
Sirolimus-stent trials									
RAVEL[1]	238	Global	Bx Velocity	Slow	2.5–3.5	<18	2	At 4 yr, 225 patients (94.5%)	At 6 mo, 211 patients (88.7%)
SIRIUS[2]	1058	United States	Bx Velocity	Slow	2.5–3.5	15–30	3	At 4 yr, 1025 patients (96.9%)	At 8 mo, 703 patients (66.4%)
E-SIRIUS[3]	352	Europe	Bx Velocity	Slow	2.5–3.0	15–32	2	At 4 yr, 344 patients (97.7%)	At 8 mo, 308 patients (87.5%)
C-SIRIUS[4]	100	Canada	Bx Velocity	Slow	2.5–3.0	15–32	2	At 4 yr, 98 patients (98.0%)	At 8 mo, 88 patients (88.0%)
Paclitaxel-stent trials									
TAXUS-I[5]	61	Germany	NIRx	Slow	3.0–3.5	≤12	6	At 4 yr, 61 patients (100.0%)	At 6 mo, 59 patients (96.7%)
TAXUS-II[6]	536	Global	NIRx	Slow and moderate	3.0–3.5	≤12	6	At 4 yr, 515 patients (96.1%)	At 6 mo, 520 patients (97.0%)
TAXUS-IV[7]	1314	United States	Express	Slow	2.5–3.75	10–28	6	At 4 yr, 1236 patients (94.1%)	At 9 mo, 559 patients (42.5%)
TAXUS-V[8]	1156	United States	Express2	Slow	2.25–4.0	10–46	6	At 2 yr, 1100 patients (95.2%)	At 9 mo, 990 patients (85.6%)
TAXUS-VI[9]	446	Europe	Express2	Moderate	2.5–3.75	18–40	6	At 3 yr, 433 patients (97.1%)	At 9 mo, 417 patients (93.5%)

* ClinicalTrials.gov numbers are as follows: RAVEL, NCT00233805; SIRIUS, NCT00232765; E-SIRIUS, NCT00235144; C-SIRIUS, NCT00381420; TAXUS-II, NCT00299026; TAXUS-IV, NCT00292474; TAXUS-V, NCT00301522; and TAXUS-VI, NCT00297804.

diac causes or myocardial infarction. The following time periods were prespecified for analysis of event rates: the time from stent implantation until 30 days after implantation, from 30 days after implantation until the latest follow-up, from 30 days after implantation until 1 year, from 1 year after implantation until the latest follow-up, and from the time of stent implantation until the latest follow-up.

We used data from the original databases, as defined and adjudicated by the clinical events committees for each study, in our analysis.[1-9] Since the individual adverse-event narratives and original source documents were not available to us, readjudication of individual events to accommodate common definitions was not possible.

STATISTICAL ANALYSIS

We compared categorical variables by the chi-square test or Fisher's exact test. Continuous variables are described as means (±SD) and were compared by means of unpaired t-tests. At the time of this report, we had access to 5-year data from RAVEL and TAXUS-I; 4-year data from SIRIUS, E-SIRIUS, C-SIRIUS, TAXUS-II, and TAXUS-IV; 3-year data from TAXUS-VI; and 2-year data from TAXUS-V. We used Kaplan–Meier time-to-event estimates for the primary analyses, which were compared with the log-rank or exact log-rank test. Analyses were truncated at 4 years of follow-up owing to the small number of patients with data thereafter. We included data from all patients that were analyzed in each of the original study reports in our analysis, with follow-up data censored at the time of first event (for each specific event curve) or latest known follow-up. The Breslow–Day test for heterogeneity demonstrated that trials involving sirolimus-eluting stents and paclitaxel-eluting stents were sufficiently homogeneous to justify the pooled analyses performed. All P values are two-sided.

RESULTS

PATIENTS

A total of 1748 patients were randomly assigned to study groups and underwent percutaneous coronary intervention in the RAVEL and three SIRIUS trials comparing sirolimus-eluting stents with bare-metal stents (the sirolimus-stent trials). Another 3513 patients were randomly assigned to study groups and underwent percutaneous coronary intervention in the five TAXUS trials comparing paclitaxel-eluting stents with bare-metal stents (the paclitaxel-stent trials). The baseline demographic, procedural, and angiographic characteristics of the patients were well matched in both sets of trials (Table 2), except that in the sirolimus-stent trials, diabetes was slightly more prevalent among patients who received bare-metal stents than among those who received sirolimus-eluting stents. The lengths of lesions and total implanted stents were both greater in the paclitaxel-stent trials than in the sirolimus-stent trials (reflecting varying criteria for trial entry), although more stents per patient were used in the sirolimus-stent trials. Baseline reference measures of vessel diameter and lesion severity were similar for stenoses treated with both types of drug-eluting stents and for those treated with bare-metal stents.

STENT THROMBOSIS

From stent implantation through 4-year follow-up, the rates of stent thrombosis among patients with sirolimus-eluting stents did not differ significantly from those with bare-metal stents (1.2% and 0.6%, respectively; P=0.20) (Table 3 and Fig. 1 and 2). Similarly, there were no significant differences in the 4-year cumulative rates of stent thrombosis between patients with paclitaxel-eluting stents and those with bare-metal stents (1.3% and 0.9%, respectively; P=0.30). However, between 1 and 4 years, the rates of stent thrombosis in the sirolimus-stent group and the bare-metal–stent group were 0.6% versus none (P=0.025, consistent with one extra event per 489 patient-years); during the same period, the rates in the paclitaxel-stent group and the bare-metal–stent group were 0.7% versus 0.2% (P=0.028, consistent with one extra event per 557 patient-years). After 1 year, of the five patients who had late thrombosis associated with sirolimus-eluting stents, two patients were taking aspirin and clopidogrel, two were taking only aspirin, and one was taking no antiplatelet agent. Of the nine patients with late thrombosis associated with paclitaxel-eluting stents, three were taking only aspirin, and five were taking no antiplatelet agent; the status of one patient is unknown.

REVASCULARIZATION

Both drug-eluting stents markedly reduced the rates of target-lesion revascularization and tar-

Table 2. Baseline Characteristics of the Patients.*

Variable	Sirolimus-Eluting Stent	Bare-Metal Stent	P Value	Paclitaxel-Eluting Stent	Bare-Metal Stent	P Value
Age — yr	61.9±11.1	61.9±10.7	0.91	62.4±10.8	62.2±10.6	0.49
Male sex — no./total no. (%)	629/878 (71.6)	622/870 (71.5)	0.96	1271/1755 (72.4)	1278/1758 (72.7)	0.88
Diabetes — no./total no. (%)						
Any type	195/878 (22.2)	233/868 (26.8)	0.03	408/1755 (23.2)	419/1758 (23.8)	0.69
Requiring insulin	51/878 (5.8)	62/868 (7.1)	0.28	127/1729 (7.3)	138/1730 (8.0)	0.52
Hypertension — no./total no. (%)	557/873 (63.8)	548/866 (63.3)	0.84	1217/1755 (69.3)	1191/1754 (67.9)	0.36
Hyperlipidemia — no./total no. (%)	613/866 (70.8)	617/859 (71.8)	0.67	1230/1744 (70.5)	1237/1751 (70.6)	0.94
Current smoker — no./total no. (%)	183/862 (21.2)	210/858 (24.5)	0.12	413/1742 (23.7)	401/1749 (22.9)	0.60
Target coronary artery — no./total no. (%)						
Left anterior descending	408/875 (46.6)	407/872 (46.7)	1.00	733/1744 (42.0)	730/1752 (41.7)	0.84
Left circumflex	181/875 (20.7)	181/872 (20.8)	1.00	444/1744 (25.5)	419/1752 (23.9)	0.31
Right coronary	254/875 (29.0)	254/872 (29.1)	1.00	560/1744 (32.1)	592/1752 (33.8)	0.30
Left main coronary	3/875 (0.3)	3/872 (0.3)	1.00	NA	NA	NA
Saphenous-vein graft	0/875	1/872 (<0.1)	0.50	NA	NA	NA
Reference vessel diameter — mm	2.72±0.45	2.72±0.48	0.98	2.74±0.51	2.74±0.51	0.83
Minimal luminal diameter — mm	0.94±0.37	0.93±0.36	0.50	0.91±0.35	0.91±0.37	0.58
Diameter stenosis — %	65.2±11.9	65.7±11.6	0.47	67.0±10.9	66.8±11.5	0.59
Lesion length — mm	13.8±5.7	13.9±5.9	0.96	15.1±7.9	15.1±8.0	0.88
No. of stents	1.42±0.69	1.39±0.61	0.38	1.21±0.48	1.19±0.46	0.19
Total stent length — mm	22.9±9.0	22.5±8.1	0.31	24.4±11.2	24.1±11.1	0.45

* Plus–minus values are means ±SD. NA denotes not applicable.

get-vessel revascularization at 4 years (Table 3). The difference in the rates of clinical restenosis peaked at approximately 1 year and then remained stable through 4 years of follow-up (Fig. 1 and 2). In the cohort of patients undergoing routine angiographic follow-up, both drug-eluting stents greatly reduced late luminal loss and binary restenosis, as compared with bare-metal stents, both in-stent (within the stent margins) and in-segment (in-stent plus 5 mm proximal and distal margins) (see the Supplementary Appendix for details).

DEATH AND MYOCARDIAL INFARCTION

The cumulative 4-year rate of death from any cause in the sirolimus-stent group did not differ significantly from that in the bare-metal–stent group (6.7% vs. 5.3%, P=0.23); the difference in rates between the paclitaxel-stent group and the bare-metal–stent group was also not significant (6.1% vs. 6.6%, P=0.68) (Table 3 and Fig. 1 and 2). Cumulative rates of death from any cause and from cardiac and noncardiac causes were also similar in both drug-eluting–stent groups and the bare-metal–stent group at 4 years (Table 3) and during each prespecified interval (Supplementary Appendix).

The cumulative 4-year rates of myocardial infarction were similar in the sirolimus-stent group and the bare-metal–stent group (6.4% vs. 6.2%, P=0.86) and in the paclitaxel-stent group and the bare-metal–stent group (7.0% vs. 6.3%, P=0.66), with no significant differences in the rates of Q-wave or non–Q-wave myocardial infarction (Table 3 and Fig. 1 and 2). The rates of myocardial infarction were also similar in both drug-

Table 3. Clinical Outcomes at 4 Years, According to Kaplan–Meier Estimates.*

Outcome	Sirolimus-Eluting Stent (N=878)	Bare-Metal Stent (N=870)	Hazard Ratio (95% CI)†	P Value‡	Paclitaxel-Eluting Stent (N=1755)	Bare-Metal Stent (N=1758)	Hazard Ratio (95% CI)†	P Value‡
	no. (%)				*no. (%)*			
Stent thrombosis								
Patients with any event	10 (1.2)	5 (0.6)	2.00 (0.68–5.85)	0.20	20 (1.3)§	14 (0.9)	1.44 (0.73–2.84)	0.30
0 to 30 days after procedure	4 (0.5)	1 (0.1)	3.98 (0.45–35.62)	0.23	8 (0.5)	10 (0.6)	0.80 (0.32–2.03)	0.79
>30 days to 4 yr after procedure	6 (0.7)	4 (0.5)	1.50 (0.42–5.30)	0.57	12 (0.8)	4 (0.3)	3.03 (0.98–9.38)	0.04
>30 days to 1 yr after procedure	1 (0.1)	4 (0.5)	0.25 (0.03–2.22)	0.18	4 (0.2)	2 (0.1)	2.01 (0.37–10.97)	0.28
>1 to 4 yr after procedure	5 (0.6)	0	NA	0.025	9 (0.7)	2 (0.2)	4.54 (0.98–21.03)	0.028
Death								
From all causes	57 (6.7)	45 (5.3)	1.27 (0.86–1.88)	0.23	86 (6.1)	92 (6.6)	0.94 (0.70–1.26)	0.68
0 to 30 days after procedure	1 (0.1)	1 (0.1)	0.99 (0.06–15.86)	1.00	2 (0.1)	5 (0.3)	0.40 (0.08–2.07)	0.43
>30 days to 4 yr after procedure	56 (6.6)	44 (5.2)	1.27 (0.86–1.89)	0.23	84 (6.0)	87 (6.3)	0.97 (0.72–1.31)	0.85
>30 days to 1 yr after procedure	10 (1.1)	6 (0.7)	1.66 (0.60–4.56)	0.32	26 (1.5)	26 (1.5)	1.00 (0.58–1.73)	0.99
>1 to 4 yr after procedure	46 (5.5)	38 (4.6)	1.21 (0.79–1.87)	0.37	58 (4.6)	61 (4.9)	0.96 (0.67–1.37)	0.81
From cardiac causes	29 (3.5)	23 (2.7)	1.26 (0.73–2.18)	0.40	36 (2.4)	42 (3.0)	0.86 (0.55–1.35)	0.51
From noncardiac causes	28 (3.3)	22 (2.7)	1.27 (0.73–2.23)	0.40	50 (3.8)	50 (3.7)	1.01 (0.68–1.49)	0.98
Myocardial infarction								
Patients with any event	55 (6.4)	53 (6.2)	1.03 (0.71–1.51)	0.86	111 (7.0)	105 (6.3)	1.06 (0.81–1.39)	0.66
0 to 30 days after procedure	22 (2.5)	17 (2.0)	1.29 (0.68–2.42)	0.43	66 (3.8)	55 (3.1)	1.20 (0.84–1.72)	0.31
>30 days to 4 yr after procedure	34 (4.1)	37 (4.4)	0.91 (0.57–1.45)	0.69	49 (3.6)	54 (3.5)	0.91 (0.62–1.34)	0.62
>30 days to 1 yr after procedure	11 (1.3)	19 (2.2)	0.57 (0.27–1.20)	0.13	14 (0.8)	31 (1.8)	0.45 (0.24–0.85)	0.01
>1 to 4 yr after procedure	23 (2.8)	18 (2.2)	1.28 (0.69–2.37)	0.43	36 (2.8)	25 (1.8)	1.45 (0.87–2.42)	0.15
Q-wave	18 (2.1)	11 (1.3)	1.64 (0.77–3.47)	0.19	22 (1.4)	17 (1.1)	1.30 (0.69–2.45)	0.42
Non–Q-wave	38 (4.5)	43 (5.0)	0.88 (0.57–1.36)	0.55	91 (5.8)	90 (5.3)	1.02 (0.76–1.36)	0.92
Death or myocardial infarction	100 (11.6)	89 (10.4)	1.12 (0.84–1.49)	0.44	187 (12.4)	183 (11.8)	1.03 (0.84–1.26)	0.79
Death or Q-wave myocardial infarction	70 (8.2)	54 (6.4)	1.30 (0.91–1.86)	0.14	105 (7.3)	107 (7.5)	0.99 (0.76–1.29)	0.93
Myocardial infarction or death from cardiac causes	75 (8.8)	70 (8.2)	1.07 (0.77–1.48)	0.69	139 (8.9)	136 (8.5)	1.03 (0.81–1.30)	0.82
Revascularization								
Target lesion	66 (7.8)	202 (23.6)	0.29 (0.22–0.39)	<0.001	166 (10.1)	338 (20.0)	0.46 (0.38–0.55)	<0.001
Target vessel	102 (12.1)	235 (27.5)	0.38 (0.30–0.48)	<0.001	272 (17.2)	409 (24.7)	0.62 (0.53–0.73)	<0.001

* Percentages are cumulative Kaplan–Meier estimates, taking into account data from patients who were lost to follow-up at different times, and may thus differ from simple binary percentages. Only the first event was counted within any interval. CI denotes confidence interval.
† The estimate was calculated from a Cox proportional-hazards model.
‡ P values were calculated by a two-sided log-rank test or exact log-rank test.
§ One patient had two episodes of stent thrombosis, one before 1 year and one after 1 year.